

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

THIS PAGE BLANK (USPTO)

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

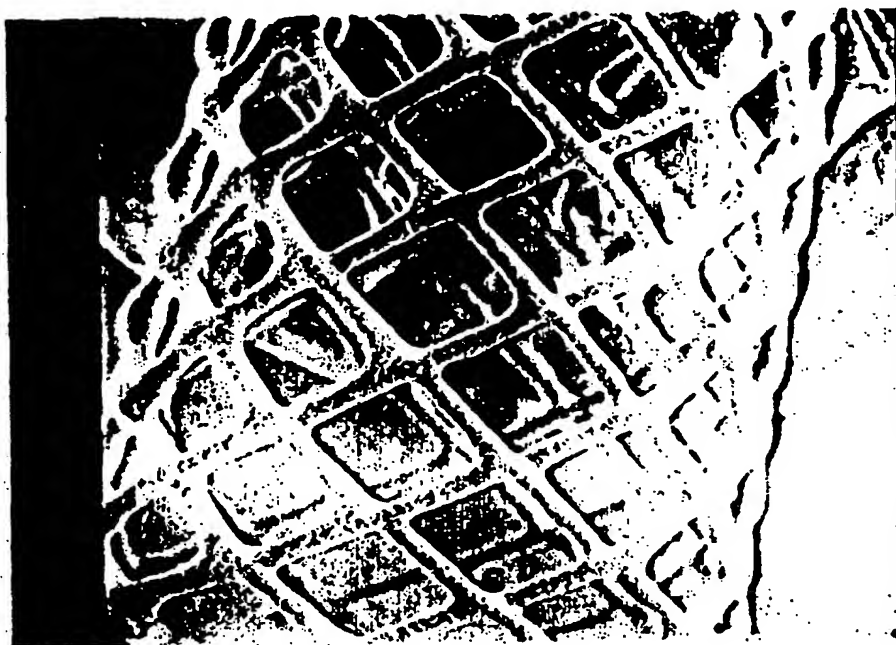


AB

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61F 2/06, A61L 31/00		A1	(11) International Publication Number: WO 96/32907
			(43) International Publication Date: 24 October 1996 (24.10.96)
(21) International Application Number: PCT/IB96/00272		(81) Designated States: AU, BR, CA, DE (Utility model), JP, KR, MX, NO, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).	
(22) International Filing Date: 1 April 1996 (01.04.96)			
(30) Priority Data: 08/424,884 19 April 1995 (19.04.95) US		Published With international search report.	
(71) Applicant: SCHNEIDER (USA) INC. [US/US]; 5905 Nathan Lane, Plymouth, MN 55442 (US).			
(72) Inventors: DING, Ni; 4365 Juneau Lane, Plymouth, MN 55446 (US). HELMUS, Michael, N.; 3722 California Avenue, Long Beach, CA 90807 (US).			
(74) Agents: SPIEGEL, Allen, J. et al.; Pfizer Inc., 235 East 42nd Street, New York, NY 10017 (US).			

(54) Title: DRUG RELEASE COATED STENT



(57) Abstract

The disclosure relates to a stent for implantation in a body lumen location of interest in a patient and includes a generally flexible elastic, tubular body (10) having open ends and a thin open porous sidewall structure and a relatively thin coating layer on the tubular body including a biostable elastomeric material incorporating an amount of biologically active material dispersed therein for timed delivery therefrom.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

DRUG RELEASE COATED STENT BACKGROUND OF THE INVENTION

I. Field of the Invention

5 The present invention relates generally to elastic, self-expanding stent prostheses for lumen, e.g., vascular, implantation and, more particularly, to the provision of biostable elastomeric coatings on such stents which incorporate elutable or diffusible biologically active species for controlled release directly in the coating structure.

II. Related Art

10 In surgical or other related invasive medicinal procedures, the insertion and expansion of stent devices in blood vessels, urinary tracts or other difficult to access places for the purpose of preventing restenosis, providing vessel or lumen wall support or reinforcement and for other therapeutic or restorative functions have become a common form of long-term treatment. Typically, such prostheses
15 are applied to a location of interest utilizing a vascular catheter, or similar transluminal device, to carry the stent to the location of interest where it is thereafter released and expanded in situ. These devices are designed primarily as permanent implants which may become incorporated in the vascular or other tissue which they contact at implantation.

20 Stent devices of the self-expanding tubular type for transluminal implantation, then, are generally known. One type of such device includes a flexible tubular body which is composed of several individual flexible thread elements each of which extends in a helix configuration with the centerline of the body serving as a common axis. A plurality of elements having the same direction
25 of winding but which are displaced axially relative to each other are provided which meet under crossing a like number of elements also so axially displaced but having the opposite direction of winding. This configuration provides a sort of braided tubular structure which assumes a stable dedicated diameter upon the relaxation but which can be reduced as for insertion by the application of axial tension which,
30 in turn, produces elongation of the body with a corresponding diameter contraction that allows the stent to be conducted through the vascular system as a narrow elongated device and thereafter allowed to expand upon relaxation at the location of interest. Prostheses of the class including a braided flexible tubular body are

illustrated and described in U.S. Patents 4,655,771 and 4,954,126 to Wallsten and 5,061,275 to Wallsten et al.

5 The general idea of utilizing implanted stents to carry medicinal agents, such as thrombolytic agents, also have been devised. U.S. Patent 5,163,952 to Froix discloses a thermal memoried expanding plastic stent device which can be formulated to carry a medicinal agent by utilizing the material of the stent itself as an inert polymeric drug carrier. Pinchuk, in U.S. Patent 5,092,877, discloses a stent of a polymeric material which may be employed with a coating associated with the delivery of drugs. Other patents which are directed to devices of the class
10 utilizing bio-degradable or bio-sorbable polymers include Tang et al, U.S. Patent 4,916,193, and MacGregor, U.S. Patent 4,994,071. A patent to Sahatjian, Patent No. 5,304,121, discloses a coating applied to a stent consisting of a hydrogel polymer and a preselected drug in which possible drugs include cell growth inhibitors and heparin. A further method of making a coated intravascular stent
15 carrying a therapeutic material in which a polymer coating is dissolved in a solvent and the therapeutic material dispersed in the solvent and the solvent thereafter evaporated is described in European patent application 0 623 354 A1 published 09 November 1994.

20 An article by Michael N. Helmus (a co-inventor of the present invention) entitled "Medical Device Design--A Systems Approach: Central Venous Catheters", 22nd International Society for the Advancement of Material and Process Engineering Technical Conference (1990) discloses surfactant-heparin complexes to be used as controlled release heparin coatings. Those polymer/drug/membrane systems require two distinct layers of function.

25 While many attempts have been made to incorporate drug delivery in conjunction with long-term catheter or implanted stent placement, for example, the associated release time has been generally, relatively short, measured in hours and days, and success has been limited. There remains a need for a comprehensive approach that provides long-term drug release, i.e., over a period
30 of weeks or months, incorporated in a controlled-release system. In addition, there is a further need with respect to incorporating a drug release coating on a metallic stent. Polymeric stents, although effective, cannot equal the mechanical properties of metal stents of a like thickness. For example, in keeping a vessel open, a

metallic stent is superior because stents braided of relatively fine metal can provide a good deal of strength to resist circumferential pressure. In order for a polymer material to provide the same strength characteristics, a much thicker-walled structure or heavier, denser filament weave is required. This, in turn, reduces the area available for flow through the stent and/or reduces the amount of porosity available in the stent. In addition, when applicable, it is more difficult to load such a stent onto catheter delivery systems for conveyance through the vascular system of the patient to the site of interest.

Accordingly, it is a primary object of the present invention to provide a coating in a deployed stent prosthesis capable of long-term delivery of biologically active materials.

Another object of the invention is to provide a coating on a deployed stent prosthesis of optimal mechanical properties with minimal surface area for long-term delivery of biologically active therapeutic materials.

Still another object of the present invention is to provide a coating on a deployed stent prosthesis using a biostable hydrophobic elastomer in which the biologically active species is incorporated within the coating.

A still further object of the invention is to provide a deployed stent prosthesis of a siloxane polymer containing crystals of heparin for dissolution via interconnected particle interstices.

A yet still further object of the present invention is to provide a braided metallic deployed stent prosthesis having a coating of a siloxane polymer material containing an amount of dissolved and/or finely divided dexamethasone.

Other objects and advantages of the present invention will become apparent to those skilled in the art upon familiarization with the specification and appended claims.

SUMMARY OF THE INVENTION

Many of the limitations of prior art implanted prolonged drug delivery systems associated with deployed stent prostheses are overcome by the provision of a relatively thin overlayer of biostable elastomeric material in which an amount of biologically active material is dispersed as a coating on the surfaces of the stent. The preferred stent is a self-expanding, open-ended tubular stent prosthesis, with a thin porous flexible elastic sidewall. Although other materials can be used

including polymer materials, in the preferred embodiment, the tubular body is formed of an open braid of fine single or polyfilament wire which flexes without collapsing and is axially deformable for insertion using a catheter or other such device but which resumes a predetermined stable diameter and length upon relaxation.

5 The coating layer is preferably applied as a mixture of polymeric precursor and finely divided biologically active species or a solution or partial solution of such species in the polymer solvent or vehicle which is thereafter cured in situ. The coating may be applied by dipping or spraying using evaporative solvent materials
10 of relatively high vapor pressure to produce the desired viscosity and coating thickness. The coating further is one which adheringly conforms to the surface of the filaments of the open structure of the stent so that the open lattice nature of the structure of the braid or other pattern is preserved in the coated device.

The elastomeric material that forms a major constituent of the stent coating
15 should possess certain properties. It is preferably a suitable hydrophobic biostable elastomeric material which does not degrade and which minimizes tissue rejection and tissue inflammation and one which will undergo encapsulation by tissue adjacent the stent implantation site. Polymers suitable for such coatings include
20 silicones (e.g., polysiloxanes and substituted polysiloxanes), polyurethanes, thermoplastic elastomers in general, ethylene vinyl acetate copolymers, polyolefin elastomers, and EPDM rubbers. The above-referenced materials are considered hydrophobic with respect to the contemplated environment of the invention.

Agents suitable for incorporation include antithrobotics, anticoagulants, antiplatelet agents, thrombolytics, antiproliferatives, antiinflammatories, agents that
25 inhibit hyperplasia and in particular restenosis, smooth muscle cell inhibitors, growth factors, growth factor inhibitors, cell adhesion inhibitors, cell adhesion promoters and drugs that may enhance the formation of healthy neointimal tissue, including endothelial cell regeneration. The positive action may come from
30 inhibiting particular cells (e.g., smooth muscle cells) or tissue formation (e.g., fibromuscular tissue) while encouraging different cell migration (e.g., endothelium) and tissue formation (neointimal tissue).

The preferred materials for fabricating the braided stent include stainless steel, tantalum, titanium alloys including nitinol (a nickel titanium, thermomemorial

alloy material), and certain cobalt alloys including cobalt-chromium-nickel alloys such as Elgiloy® and Phynox®. Further details concerning the fabrication and details of other aspects of the stents themselves, may be gleaned from the above referenced U.S. Patents 4,655,771 and 4,954,126 to Wallsten and 5,061,275 to Wallsten et al. To the extent additional information contained in the above-
5 referenced patents is necessary for an understanding of the present invention, they are deemed incorporated by reference herein.

Various combinations of polymer coating materials can be coordinated with biologically active species of interest to produce desired effects when coated on
10 stents to be implanted in accordance with the invention. Loadings of therapeutic materials may vary. The mechanism of incorporation of the biologically active species into the surface coating, and egress mechanism depend both on the nature of the surface coating polymer and the material to be incorporated. The mechanism of release also depends on the mode of incorporation. The material
15 may elute via interparticle paths or be administered via transport or diffusion through the encapsulating material itself.

The desired release rate profile can be tailored by varying the coating thickness, the radial distribution of bioactive materials, the mixing method, the amount of bioactive material, and the crosslink density of the polymeric material.
20 The crosslink density is related to the amount of crosslinking which takes place and also the relative tightness of the matrix created by the particular crosslinking agent used. This, after the curing process, determines the amount of crosslinking and so the crosslink density of the polymer material. For bioactive materials released from the crosslinked matrix, such as heparin, a denser crosslink structure
25 will result in a longer release time and small burst effect.

BRIEF DESCRIPTION OF THE DRAWINGS

In the drawings, wherein like numerals designate like parts throughout the same:

FIGURES 1 and 1A depict greatly enlarged views of a fragment of a
30 medical stent for use with the coating of the invention;

FIGURES 2A and 2B depict a view of a stent section as pictured in Figures 1 and 1A as stretched or elongated for insertion;

FIGURE 3 is a light microscopic photograph of a typical uncoated stent structure configuration (20X);

FIGURE 4A is a scanning electron microscope photograph (SEM) of a heparin containing poly siloxane coating on a stent in accordance with the invention (X20) after release of heparin into buffer for 49 days;

FIGURE 4B is a higher powered scanning electron microscopic photograph (SEM) of the coating of Figure 4A (X600);

FIGURE 5A is another scanning electron microscopic photograph (SEM) of a different stent coated with coating as produced with heparin incorporated into the polysiloxane (X20);

FIGURE 5B is an enlarged scanning electron microscopic photograph (SEM) of the coating of Figure 5B (X600);

FIGURE 6A is a light microscopic picture (X17.5) of a histologic cross-section of a silicone/heparin coated stent implanted in a swine coronary for 1 day;

FIGURE 6B depicts a pair of coated filaments of the stent of Figure 6A (X140) showing the open porous structure of the silicone;

FIGURE 7A is a scanning electron microscope photograph (SEM) that depicts a polysiloxane coating containing 5% dexamethasone (X600);

FIGURE 7B depicts the coating of Figure 7A (SEM X600) after dexamethasone release in polyethylene glycol (PEG 400/H₂O) for three months;

FIGURE 8 is a plot showing the total percent heparin released over 90 days from a coated stent in which the coated layer is 50% heparin (based on the total weight of the coating) in a silicone polymer matrix; release took place in phosphoric buffer (pH=7.4) at 37°C; and

FIGURE 9 is a plot of the total percent dexamethasone released over 100 days for two percentages of dexamethasone in silicon coated stents; release took place in polyethylene glycol (PEG), MW=400 (PEG 400/H₂O, 40/60, vol/vol) at 37°C.

DETAILED DESCRIPTION

A type of stent device of one class designed to be utilized in combination with coatings in the present invention is shown diagrammatically in a side view and an end view, respectively contained in Figures 1A and 1B. Figure 1A shows a broken section of a generally cylindrical tubular body 10 having a mantle surface

formed by a number of individual thread elements 12, 14 and 13, 15, etc. of these elements, elements 12, 14, etc. extend generally in an helix configuration axially displaced in relation to each other but having center line 16 of the body 10 as a common axis. The other elements 13, 15, likewise axially displaced, extend in
5 helix configuration in the opposite direction, the elements extending in the two directions crossing each other in the manner indicated in Figure 1A. A tubular member so concerned and so constructed can be designed to be any convenient diameter, it being remembered that the larger the desired diameter, the larger the number of filaments of a given wire diameter (gauge) having common composition
10 and prior treatment required to produce a given radial compliance.

The braided structure further characteristically readily elongates upon application of tension to the ends axially displacing them relative to each other along center line 16 and correspondingly reducing the diameter of the device. This is illustrated in Figures 2A and 2B in which a segment of the device 10 of
15 Figures 1A and 1B has been elongated by moving the ends 18 and 20 away from each other in the direction of the arrows. Upon the release of the tension on the ends, the structure 10, if otherwise unrestricted, will reassume the relaxed or unloaded configuration of Figures 1A and 1B.

The elongation/resumption characteristic flexibility of the stent device
20 enables it to be slipped or threaded over a carrying device while elongated for transportation through the vascular or other relevant internal luminal system of a patient to the site of interest where it can be axially compressed and thereby released from the carrying mechanism, often a vascular catheter device. At the site of interest, it assumes an expanded condition held in place by
25 mechanical/frictional pressure between the stent and the lumen wall against which it expands.

The elongation, loading, transport and deployment of such stents is well known and need not be further detailed here. It is important, however, to note that
30 when one contemplates coatings for such a stent in the manner of the present invention, an important consideration resides in the need to utilize a coating material having elastic properties compatible with the elastic deforming properties residing in the stent that it coats. The material of the stent should be rigid and elastic but not plastically deformable as used. As stated above, the preferred

materials for fabricating the metallic braided stent include stainless steel, tantalum, titanium alloys including nitinol and certain cobalt-chromium alloys. The diameter of the filaments may vary but for vascular devices, up to about 10 mm in diameter is preferable with the range 0.01 to 0.05 mm.

5 Drug release surface coatings on stents in accordance with the present invention can release drugs over a period of time from days to months and can be used, for example, to inhibit thrombus formation, inhibit smooth muscle cell migration and proliferation, inhibit hyperplasia and restenosis, and encourage the formation of health neointimal tissue including endothelial cell regeneration. As
10 such, they can be used for chronic patency after an angioplasty or stent placement. It is further anticipated that the need for a second angioplasty procedure may be obviated in a significant percentage of patients in which a repeat procedure would otherwise be necessary. A major obstacle to the success of the implant of such stents, of course, has been the occurrence of thrombosis in certain
15 arterial applications such as in coronary stenting. Of course, antiproliferative applications would include not only cardiovascular but any tubular vessel that stents are placed including urologic, pulmonary and gastro-intestinal.

Various combinations of polymer coating materials can be coordinated with the braided stent and the biologically active agent of interest to produce a
20 combination which is compatible at the implant site of interest and controls the release of the biologically active species over a desired time period. Preferred coating polymers include silicones (poly siloxanes), polyurethanes, thermoplastic elastomers in general, ethylene vinyl acetate copolymers, polyolefin rubbers, EPDM rubbers, and combinations thereof.

25 Specific embodiments of the present invention include those designed to elute heparin to prevent thrombosis over a period of weeks or months or to allow the diffusion or transport of dexamethasone to inhibit fibromuscular proliferation over a like period of time. Of course, other therapeutic substances and combinations of substances are also contemplated. The invention may be
30 implanted in a mammalian system, such as in a human body.

The heparin elution system is preferably fabricated by taking finely ground heparin crystal, preferably ground to an average particle size of less than 10 microns, and blending it into a liquid, uncured poly siloxane/solvent material in

which the blend (poly siloxane plus heparin) contains from less than 10% to as high as 80% heparin by weight with respect to the total weight of the material and typically the layer is between 10% and 45% heparin.

5 This material is solvent diluted and utilized to coat a metallic braided stent, which may be braided cobalt chromium alloy wire, in a manner which applies a thin, uniform coating (typically between 20 and 200 microns in thickness) of the heparin/polymer mixture on the surfaces of the stent. The polymer is then heat cured, or cured using low temperature thermal initiators ($<100^{\circ}\text{C}$) in a room temperature vulcanization (RTV) process in situ on the stent evaporating solvent, 10 typically tetrahydrofuran (THF) with the heparin forming interparticle paths in the silicone sufficiently interconnected to allow slow but substantially complete subsequent elution. The ultrafine particle size utilized allows the average pore size to be very small such that elution may take place over weeks or even months.

15 A coating containing dexamethasone is produced in a somewhat different manner. A poly siloxane material is also the preferred polymeric material. Nominally an amount equal to 0.4% to about 45% of the total weight of the layer of dexamethasone is used.

20 The dexamethasone drug is dissolved in a solvent, e.g., THF first. The solution is then blended into liquid uncured poly siloxane/solvent (xylene, THF, etc.) vehicle precursor material. Since the dexamethasone is also soluble in the solvent for the polysiloxane, it dissolves into the mixture. The coating is then applied to the stent and upon application, curing and drying, including evaporation of the solvent, the dexamethasone remains dispersed in the coating layer. It is believed that the coating is somewhat in the nature of a solid solution of 25 recrystallized particles of dexamethasone in silicone rubber. Dexamethasone, as a rather small molecule, however, does not need gross pores to elute and may be transported or diffused outward through the silicone material over time to deliver its anti-inflammatory medicinal effects.

30 The coatings can be applied by dip coating or spray coating or even, in some cases, by the melting of a powdered form in situ or any other technique to which the particular polymer/biologically active agent combination is well suited.

It will be understood that a particularly important aspect of the present invention resides in the technology directed to the incorporation of very fine

microparticles or colloidal suspensions of the drug into the polymer matrix. In the case of a crystalline drug, such as heparin, the drug release is controlled by the network the drug forms in the polymer matrix, the average particulate size controlling the porosity and so the ultimate elution rate.

5 Figure 4A depicts a stent which has been spray coated with a solvent containing a cured polysilicone material including an amount of heparin crystals to provide a thin, uniform coating on all surfaces of the stent. The coated stent was cured at 150°C for 18 minutes; The sample was eluted in PBS for 49 days at 37°C and the stent was rinsed in ethanol prior to taking the scanning electron
10 microscope picture of Figure 4A. Figure 4B shows a greatly enlarged (600X) scanning electron microscope photograph (SEM) of a portion of the coating of Figure 4A in which the microporosity is evident. The coating thickness may vary but is typically from about 75 to about 200 microns.

15 Figures 5A and 5B show scanning electron microscope photographs of a heparin containing polysiloxane stent. The Figure shows the coating prior to elution of the heparin. The coating was cured at 150° for 18 minutes. Figure 5B is greatly enlarged photograph (SEM) of a fragment of the coated surface of Figure 5A showing the substantially non-porous surface prior to elution.

20 Figures 6A and 6B show the posture of a stent in accordance with the invention as implanted in a swine coronary. The blemish shown in Figure 6A represents a histological artifact of unknown origin. As can be seen in Figure 6B, the general texture of the heparin-containing silicone material appears as a relatively open matrix containing a large number of gross pores.

25 The substantially non-porous surface of Figure 7A typically occurs with an incorporation of an amount of non-particulate material such as dexamethasone which partially or entirely dissolves in the solvent for the poly siloxane prior to coating and cure. Upon curing of the polymer and evaporation of the solvent, depending on the loading of dexamethasone, the dexamethasone reprecipitates in a hydrophobic crystalline form containing dendrite or even elongated hexagonal
30 crystals approximately 5 microns in size.

As can be seen in Figure 7B, even after release of the incorporated material or three months, the coating surface remains substantially non-porous indicating the transport or diffusion of the drug outward through the silicone

material neither requires nor produces gross pores. The dexamethasone is incorporated in its more hydrophobic form rather than in one of the relatively more hydrophilic salt forms such as in a phosphate salt, for example.

Figures 8 and 9 depict plots of total percent drug release related to long-term drug release stent coating layers. Figure 8 depicts the release of heparin from a 50% heparin loading in silicone. The silicone was cured at 90°C for 16 hours. The heparin release took place in a phosphoric buffer (pH=7.4) for 90 days at 37°C. The heparin concentration in the phosphoric buffer was analyzed by Azure A assay.

Figure 9 depicts a graphical analysis, similar to that depicted for heparin in Figure 8, for the release of dexamethasone at two different concentrations, i.e., 5% and 10% in silicone polymer. The coated stents were cured at 150°C for 20 minutes and the release took place in a polyethylene glycol (PEG), MW=400/water solution at 37°C ((PEG 400/H₂O) (40/60, vol/vol)). The dexamethasone concentrations were analyzed photometrically at 241 µm.

Figures 8 and 9 illustrate possible stent layer polymer/bioactive species combinations for long-term release. As stated above, the release rate profile can be altered by varying the amount of active material, the coating thickness, the radial distribution of bioactive materials, the mixing method, and the crosslink density of the polymer matrix. Sufficient variation is possible such that almost any reasonable desired profile can be simulated.

As stated above, while the allowable loading of the elastomeric material with heparin may vary in the case of silicone materials, heparin may exceed 60% of the total weight of the layer. However, the loading generally most advantageously used is in the range from about 10% to 45% of the total weight of the layer. In the case of dexamethasone, the loading may be as high as 50% or more of the total weight of the layer but is preferably in the range of about 0.4% to 45%.

It will be appreciated that the mechanism of incorporation of the biologically active species into a thin surface coating structure applicable to a metal stent is an important aspect of the present invention. The need for relatively thick-walled polymer elution stents or any membrane overlayers associated with many prior drug elution devices is obviated, as is the need for utilizing biodegradable or

reabsorbable vehicles for carrying the biologically active species. The technique clearly enables long-term delivery and minimizes interference with the independent mechanical or therapeutic benefits of the stent itself.

5 Coating materials are designed with a particular coating technique, coating/drug combination and drug infusion mechanism in mind. Consideration of the particular form and mechanism of release of the biologically active species in the coating allow the technique to produce superior results. In this manner, delivery of the biologically active species from the coating structure can be tailored to accommodate a variety of applications.

10 Whereas the polymer of the coating may be any compatible biostable elastomeric material capable of being adhered to the stent material as a thin layer, hydrophobic materials are preferred because it has been found that the release of the biologically active species can generally be more predictably controlled with such materials. Preferred materials include silicone rubber elastomers and
15 biostable polyurethanes specifically.

This invention has been described herein in considerable detail in order to comply with the Patent Statutes and to provide those skilled in the art with the information needed to apply the novel principles and to construct and use
20 embodiments of the example as required. However, it is to be understood that the invention can be carried out by specifically different devices and that various modifications can be accomplished without departing from the scope of the invention itself.

CLAIMS

We claim:

1. A stent for implantation in a body comprising a tubular metal body (10) having open ends and an open lattice sidewall structure and a layer on the surface of said sidewall structure, said layer comprising a hydrophobic elastomeric material incorporating an amount of biologically active material therein for timed delivery therefrom.

2. The device of Claim 1 wherein said tubular body (10) is formed of an open braid of filaments (12,13,14,15) of fine metallic wire which is axially deformable for insertion but which resumes a predetermined diameter and length upon relaxation.

3. The device of Claim 2 wherein the metal is selected from the group consisting of stainless steel, titanium alloys including nitinol, tantalum, and cobalt-chrome alloys.

4. The device of Claim 1 wherein said layer is applied as a solvent mixture of uncured polymeric material and finely divided biologically active species and then cured at an elevated temperature.

5. The device of Claim 4 wherein the biostable elastomeric material is selected from the group consisting of silicones, polyurethanes, ethylene vinyl acetate copolymers, polyolefin elastomers, EPDM rubbers and combinations thereof.

6. The device of Claim 1 wherein said elastomeric material is a poly siloxane and wherein said biologically active material is selected from the group consisting of heparin and dexamethasone.

7. The device of Claim 6 wherein said biologically active material is heparin having an average particle size 10 microns.

8. The device of Claim 7 wherein the amount of heparin is from about 10% to about 45% of the total weight of the layer.

9. The device of Claim 7 wherein said layer is from about 30 to about 150 μm in thickness.

10. The device of Claim 4 wherein said biologically active species is at least partially soluble in said solvent mixture of uncured polymeric material.

11. The device of Claim 10 wherein said biologically active species is dexamethasone and comprises from about 0.4% to about 45% of the total weight of the layer.

12. The device of Claim 2 wherein said coating adheres to the filaments
5 (12,13,14,15) of fine metallic wire in a manner that preserves said open braid.

13. The device of Claim 6 wherein said coating adheres to the filaments
(12,13,14,15) of fine metallic wire in a manner that preserves said open braid.

14. A tubular stent for implantation in a body lumen location of interest
10 comprising a flexible, elastic open braided tubular body (10) of relatively fine metallic wire, said body being coated with a thin layer of a biostable hydrophobic biologically inactive elastomeric material selected from the group consisting of silicones, polyurethanes, thermoplastic elastomers, ethylene vinyl acetate
15 copolymers, and EPDM rubbers, containing an amount of finely divided biologically active material dispersed therein in a manner that produces a controlled delivery of said biologically active species from said stent upon implantation, said coating
adhering to the individual filaments (12,13,14,15) of said braided structure in a manner that preserves said open braided structure.

15. A stent for implantation in a body comprising a tubular metal body
(10) having open ends and an open lattice sidewall structure and a layer on the
20 surface of said sidewall structure, said layer comprising a hydrophobic elastomeric material containing biologically active material therein, the layer adapted to provide long-term delivery of said biologically active material in the body.

16. The device of Claim 15 wherein the hydrophobic elastomeric
material is selected from the group of silicones, polyurethanes, ethylene vinyl
25 acetate copolymers, polyolefin elastomers, and EPDM rubbers and combinations thereof.

17. The device of Claim 15 wherein said elastomeric material is a poly
siloxane and wherein said biologically active material is selected from the group
consisting of heparin and dexamethasone.

30 18. The device of Claim 15 wherein said biologically active material is heparin having an average particle size 10 microns.

19. The device of Claim 15 wherein said biologically active species is dexamethasone and comprises from about 0.5% to about 10% by weight of said coating.

5 20. The device of Claim 15 wherein said tubular body (10) is formed of an open braid of filaments (12,13,14,15) of fine metallic wire, and said coating adheres to the filaments (12,13,14,15) of fine metallic wire in a manner that preserves said open braid.

FIG. 1A

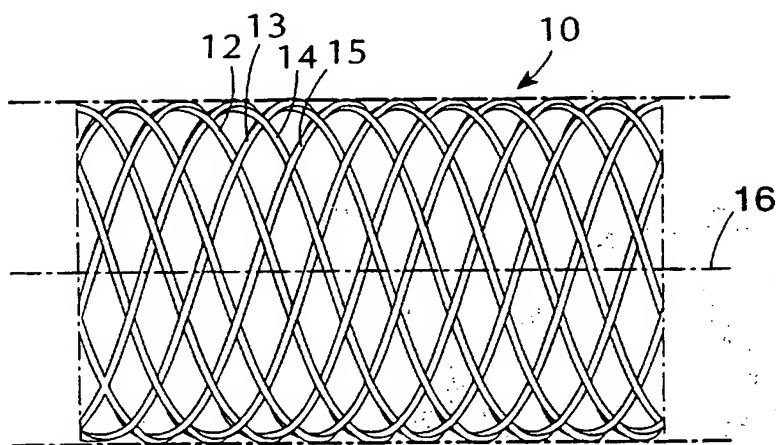


FIG. 1B

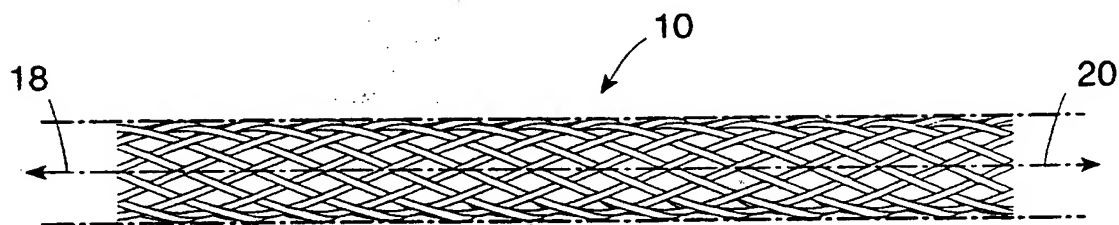
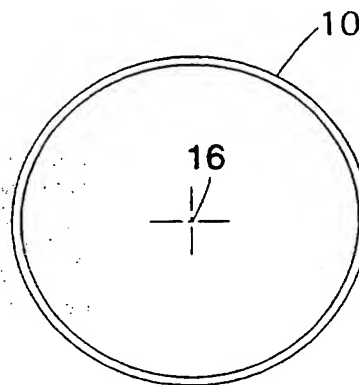


FIG. 2A

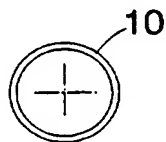


FIG. 2B

FIG. 3



FIG. 4A

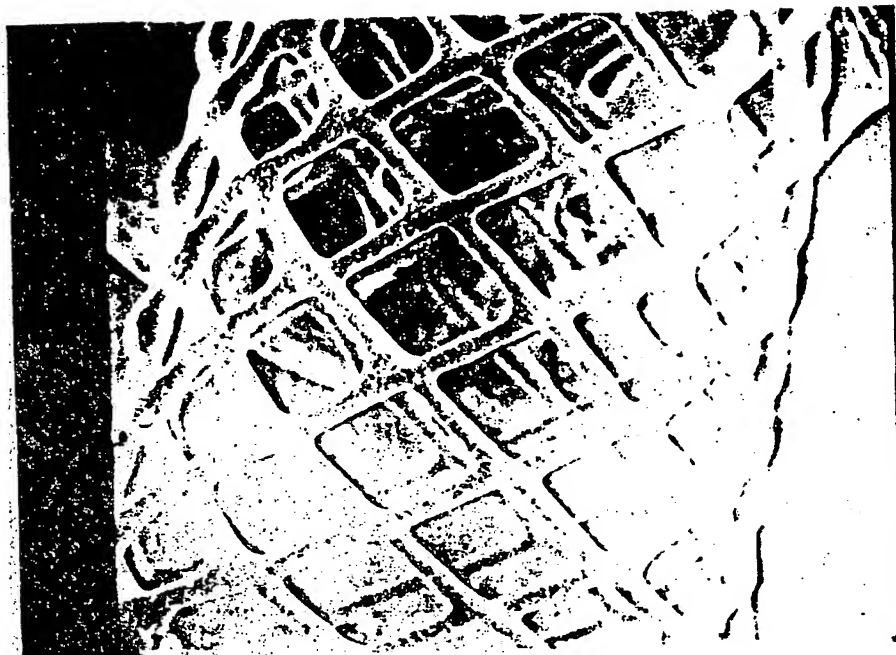
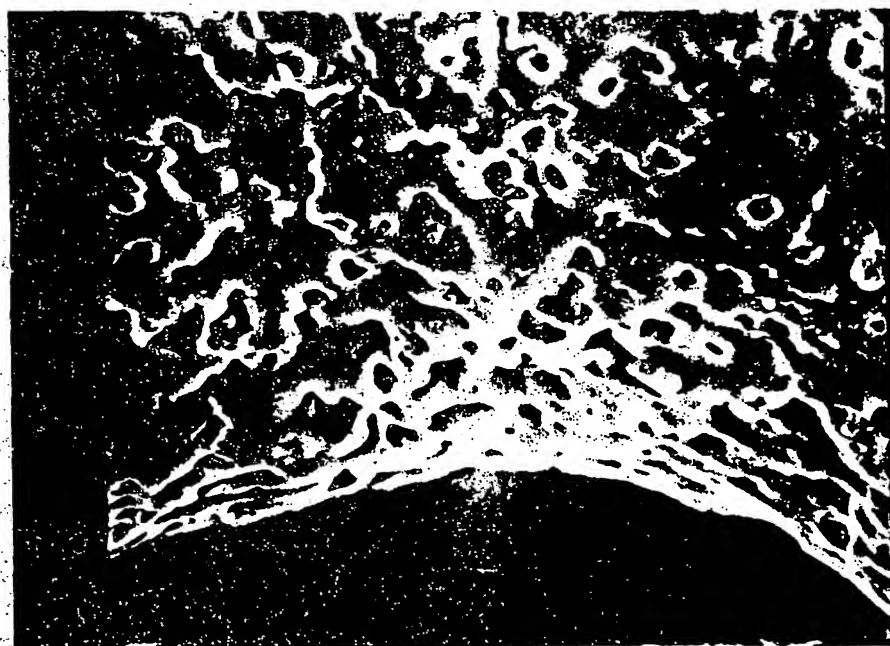


FIG. 4B



4/7

FIG. 5A

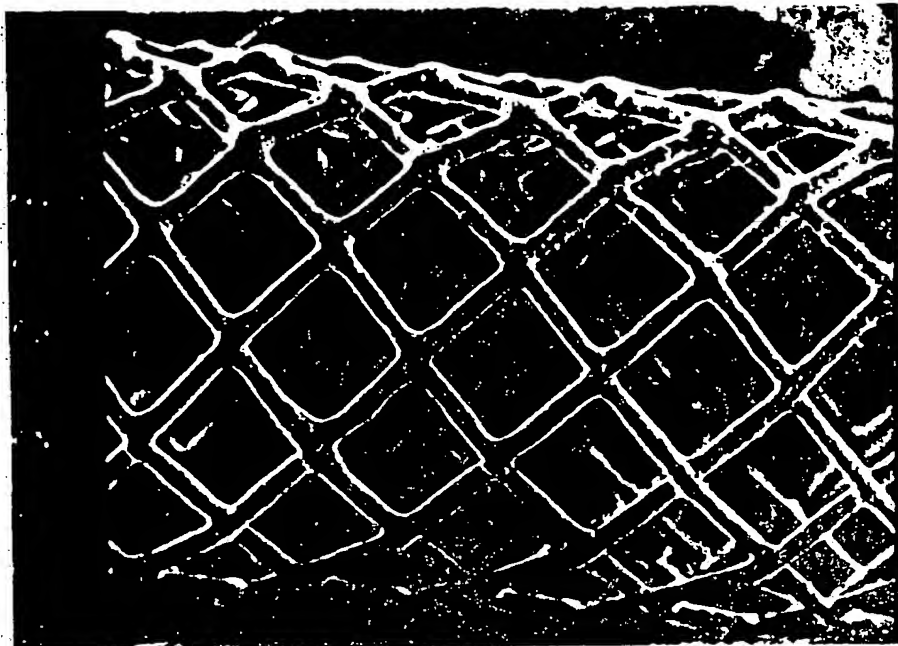


FIG. 5B

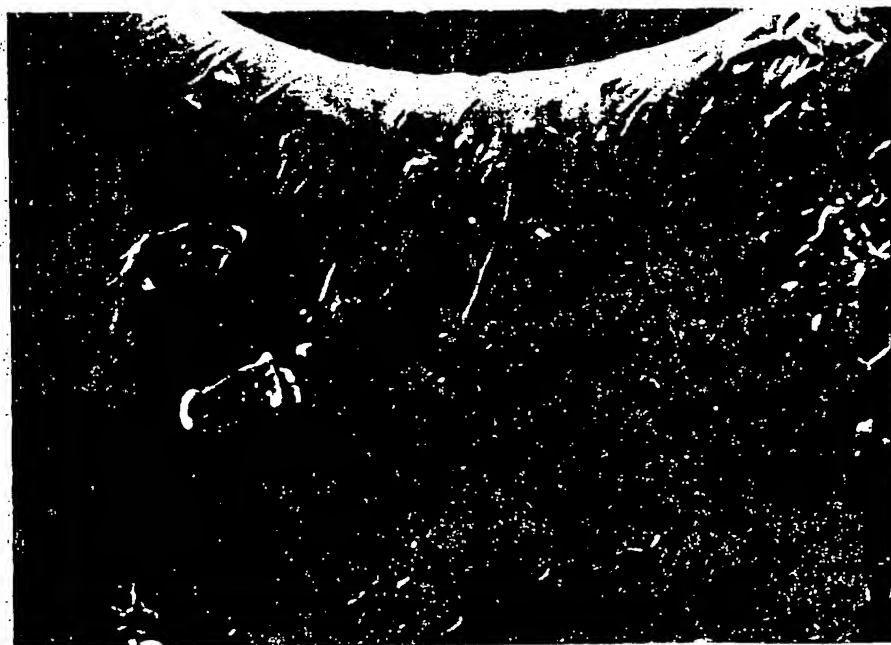


FIG. 6A

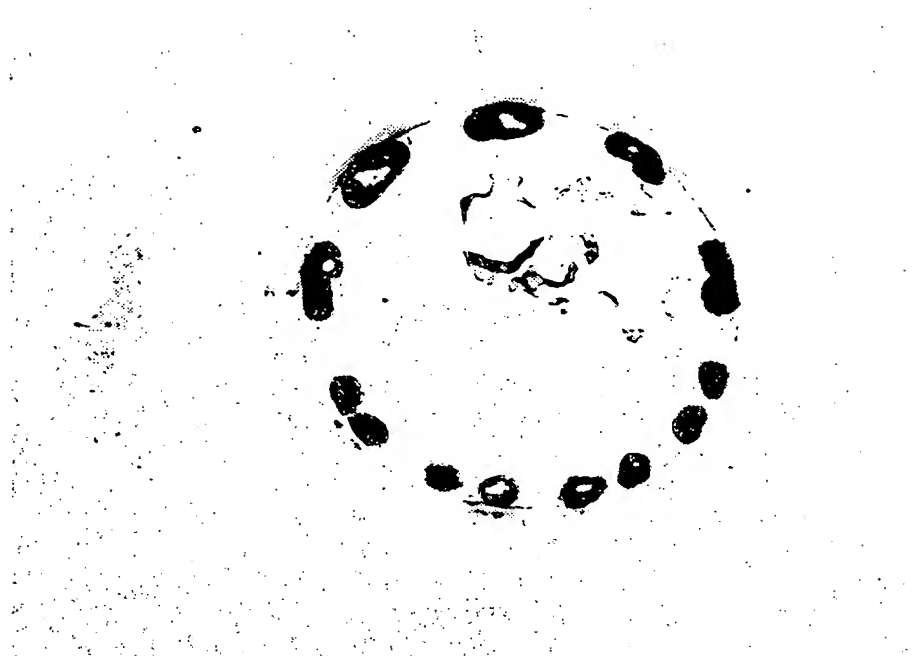
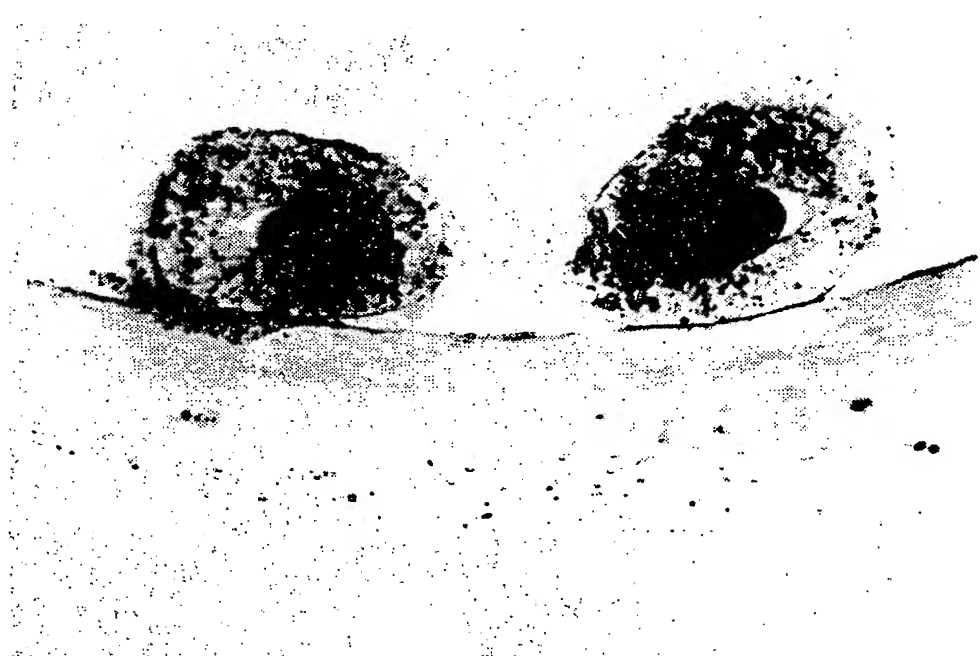


FIG. 6B



6/7

FIG. 7A

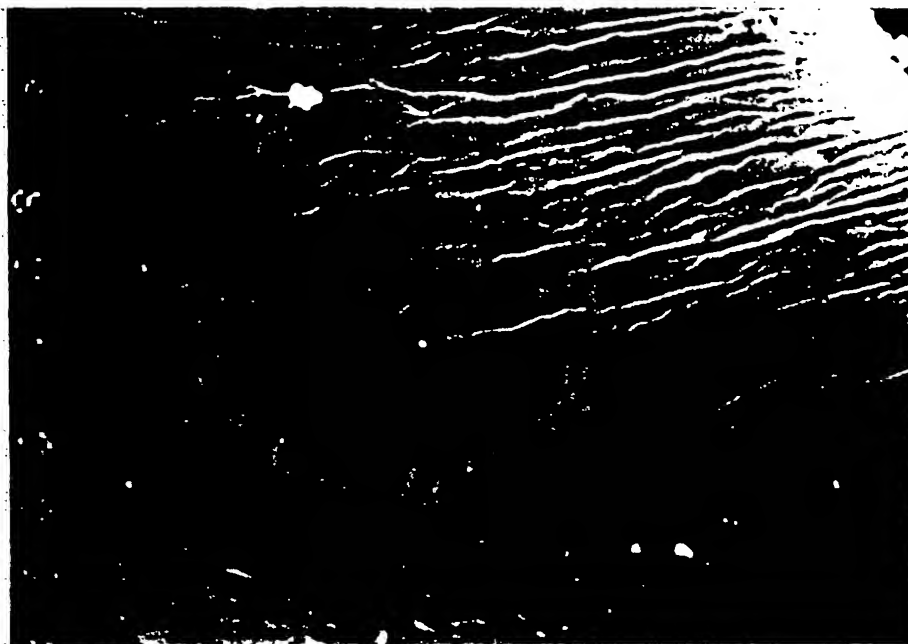
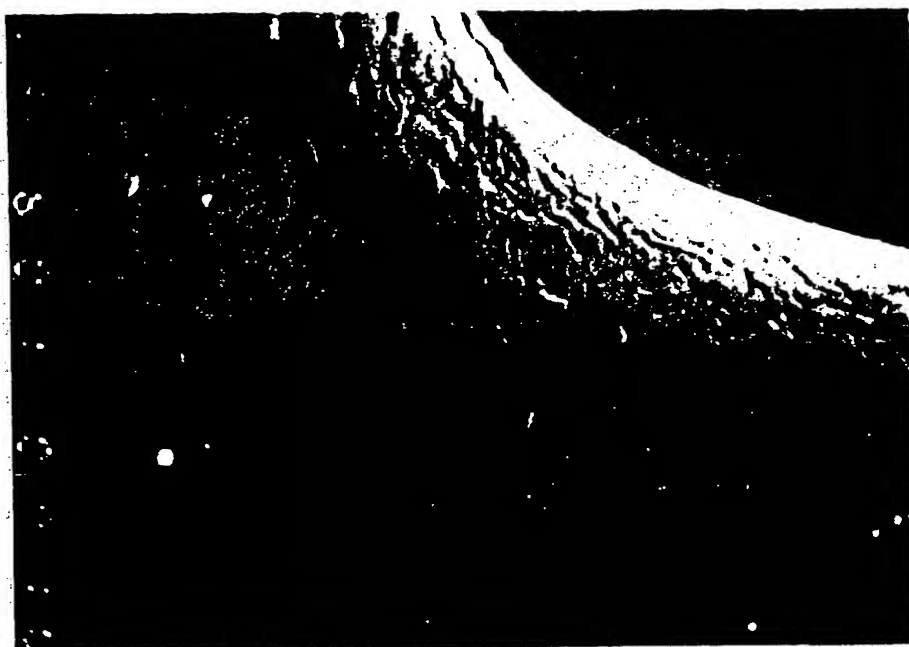


FIG. 7B



7/7

FIG. 8

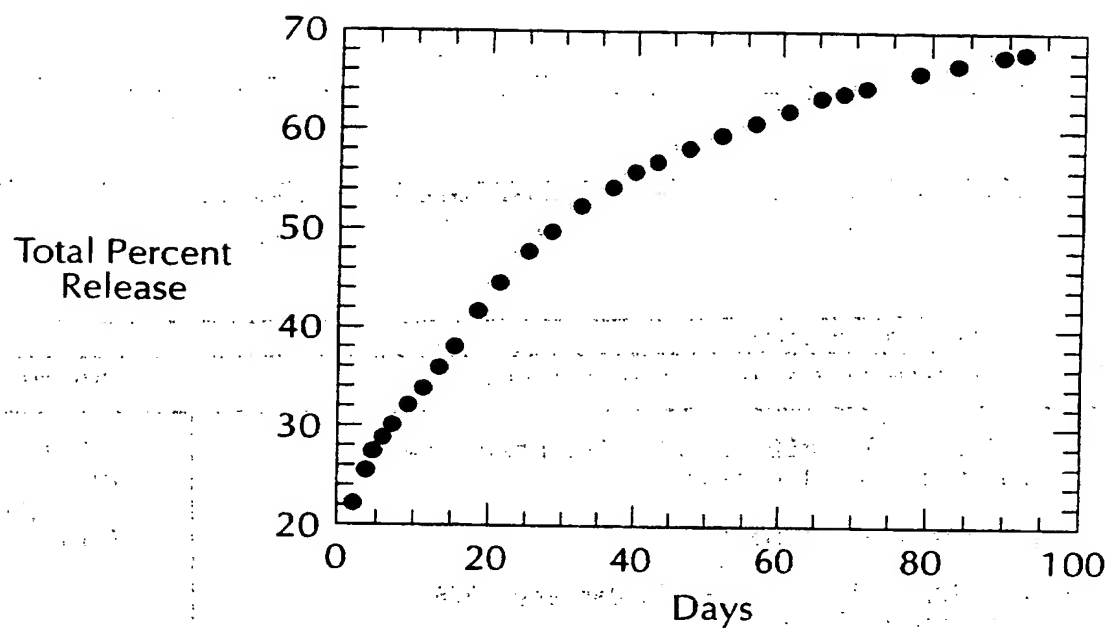
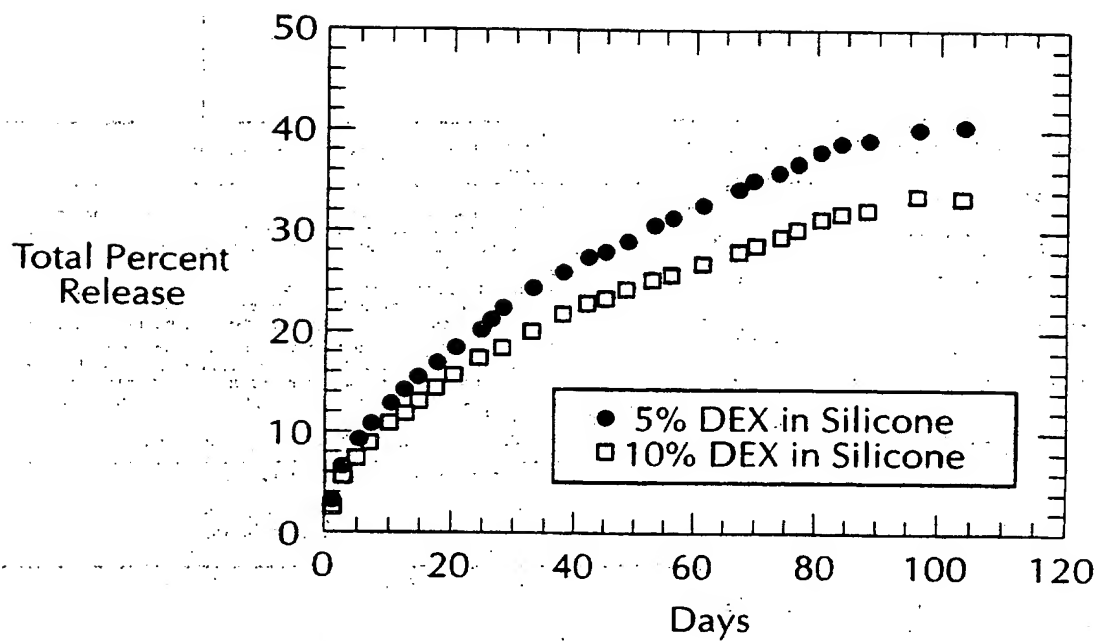


FIG. 9



INTERNATIONAL SEARCH REPORT

Int. Appl. No.

PCT/IB 96/00272

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61F2/06 A61L31/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61F A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 623 354 (MEDTRONIC) 9 November 1994 cited in the application	1-6,9, 10, 12-17,20
Y	see the whole document	7,18
Y	US,A,3 932 627 (MARGRAF) 13 January 1976 see column 2, line 1-9	7,18
A	WO,A,91 12779 (MEDTRONIC) 5 September 1991 see page 10, line 31-38	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- * "A" document defining the general state of the art which is not considered to be of particular relevance
- * "E" earlier document but published on or after the international filing date
- * "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- * "O" document referring to an oral disclosure, use, exhibition or other means
- * "P" document published prior to the international filing date but later than the priority date claimed

- * "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- * "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- * "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- * "&" document member of the same patent family

Date of the actual completion of the international search

17 June 1996

Date of mailing of the international search report

26.06.96

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+ 31-70) 340-3016

Authorized officer

Steenbakker, J

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/IB 96/00272

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-623354	09-11-94	US-A- 5464650 JP-A- 8033718	07-11-95 06-02-96
US-A-3932627	13-01-76	NONE	
WO-A-9112779	05-09-91	DE-D- 69110787 DE-T- 69110787 EP-A- 0470246 JP-T- 5502179	03-08-95 04-04-96 12-02-92 22-04-93